What is the relationship between consumption of seafood n-3 fatty acids and the risk of cardiovascular disease?

Conclusion

Moderate evidence shows that consumption of two servings of seafood per week (4oz per serving), which provide an average of 250mg per day of long-chain n-3 fatty acids, is associated with reduced cardiac mortality from coronary heart disease (CHD) or sudden death in persons with cardiovascular disease (CVD).

Grade: Moderate

Overall strength of the available supporting evidence: Strong; Moderate; Limited; Expert Opinion Only; Grade not assignable For additional information regarding how to interpret grades, click here.

Evidence Summary Overview

The 2010 Dietary Guidelines Advisory Committee (DGAC) conducted a full Nutrion Evidence Library (NEL) search of the literature from 2004 to evaluate the association of seafood consumption andcardiovascular disease (CVD) risk. Results of this review were supplemented by an earlier evidence review of the literature from 2004 to 2007 conducted by the American Dietetic Association (ADA) on health benefits related to consumption of fish or fish-derivedomega-3 fatty acids (n-3 FAs) in subjects without or with CVD. Taken together, the NEL and ADA evidence reviews identified 28 studies published since 2004 assessing the health benefits of seafood consumption in persons without CVD. These included seven systematic reviews and meta-analyses, including four methodologically strong reviews with meta-analyses of randomized controlled trials (RCTs) and prospective cohort studies (He, 2004; Konig, 2005; Mozaffarian, 2008; Mozaffarian and Rimm, 2006), one methodologically strongsystematic review of 14 RCTs, 25 prospective cohort studies and seven case-control studies (Wang, 2006) and one methodologically neutral meta-analysis of 14 cohort and five case-control studies (Whelton, 2004). These also included four RCTs ranging in size from 33 to 48 subjects conducted in the US and Finland, including two methodologically strong studies (Lara, 2007; Seierstad, 2005) and two methodologically neutral studies (Lindqvist, 2009; Lankinen, 2009). Lastly, this included 15 prospective cohort studies conducted in the US, Europe, Japan and China, ranging in size from 300 to 57,972 subjects, including eight methodologically strong (Brouwer, 2006; Frost and Vestergaard, 2005; Iso, 2006 ; Järvinen, 2006; Mozaffarian, 2004; Mozaffarian, 2005; Virtanen, 2008; Virtanen, 2009) and seven methodologically neutral studies (Albert, 2002; Folsom and Demissie, 2005; Levitan, 2009; Pangiotakos, 2007; Streppel, 2008; Turunen, 2008; Yamagishi, 2008).

Three of the systematic reviews assessed both fish and long-chain n-3 FAs (Mozaffarian, 2008; Mozaffarian and Rimm, 2007; Wang, 2006) and three meta-analyses covered only fish (Konig, 2005; Whelton, 2004; and He, 2004). The systematic reviews and meta-analyses were consistent in showing that fatty fish consumption at about two servings per week [about 250mg eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) per day] decreases risk of CVD events. Intakes above this level appeared to result in no significant (NS) additional decreases in risk CVD.

The RCT evidence showed an inverse protective association between fish intake and intermediate markers of CVD risk and CVD health outcomes. The interventions were fish-specific and included the following:

- One study that showed herring significantly increased serum high-density lipoprotein cholesterol (HDL-C) levels (Lindqvist, 2009)
- Two studies on salmon that showed salmon vs. no fish intake improved serum lipids and blood pressure (BP) (Lara, 2006) and intake of salmon with different levels of EPA + DHA showed the high EPA+DHA salmon improved serum lipids and markers of inflammation (Seierstad, 2005)
- One study comparing fatty vs. lean fish showed that fatty fish consumption improved serum lipid profiles and markers of insulin resistance and inflammation (Lankinen, 2006).

Evidence from prospective cohort studies was substantial and focused on primary CVD prevention in healthy adults. Ten prospective cohort studies examined the association between fatty fish and CVD outcomes and found a positive association between seafood and seafood-derived n-3 fatty acid consumption and decreased CVD incidence or risk (Levitan, 2009; Virtanen, 2008; Yamagishi, 2008; Streppel, 2008; Turunen, 2008; Järvinen, 2006; Iso, 2006; Mozaffarian, 2005; Lemaitre, 2003; Albert, 2002). Three prospective cohort studies examined fish and fish-derived fatty acid consumption and atrial fibrillation and found either no association between fish n-3 fatty acid intake and reduced risk of atrial fibrillation (Brouwer, 2006; Frost and Vestergaard, 2005) or a inverse association between consumption of tuna or other broiled or baked fish (but not fried fish) and incidence of atrial fibrillation (Mozaffarian, 2004). Virtanen et al, (2009) reported n-3 fatty acids (especially DHA) to be effective in reducing atrial fibrillation in men.

One prospective cohort study examined the association between fatty fish intake and intermediate markers of CVD risk and found moderate intake of fatty fish was inversely associated with serum lipids and BP (Panagiotakos, 2007). One prospective cohort study assessed fish n-3 FA intake on CVD and coronary heart disease (CHD) mortality and found no independent association with CHD or stroke mortality (Folsom and Demissie, 2005). One prospective cohort study found a positive association between fish intake and increased incidence of T2D (Kaushik, 2009). This is the only observational evidence regarding risk of T2D, but the RCT on fatty vs. lean fish by Lankinen et al, (2009) examined markers of insulin resistance and can be added to the evidence regarding T2D.

The 2005 DGAC indicated there was sufficient evidence to suggest that n-3 PUFA consumption provided protection for persons with existing CVD. For the current 2010 review, conclusions related to persons with CVD relied on the ADA evidence-based review referred to above, as a NEL search did not yield additional studies that met the inclusion criteria. Four studies were reviewed by the ADA that addressed the relationship between consumption of fish-derived n-3 fatty acids and risk of CVD events in persons with CVD. One was a methodologically strong meta-analysis covering 11 RCTs (Bucher, 2002) and three studies were methodologically strong prospective cohort studies conducted in the US with cohort size ranging from 228 to 415 subjects (Erkkila, 2003, 2004, 2006).

Evidence Summary Paragraphs

Systematic reviews/Meta-analyses

Bucher et al, 2002 (positive-quality) meta-analysis, assessed the effects of dietary and non-dietary (supplemental) intake of N-3 PUFA on CHD. Eleven studies were included: Two dietary intervention trials (intervention group N=57, control group N=58) and nine supplementation trials with N-3 PUFAs (N=7,894 in intervention groups, N=7,797 in control groups). No description of fish intake was provided. For non-fatal myocardial infarction (MI), the risk ratio in two trials of dietary intervention compared with controls was 0.8 (95% CI: 0.5 to 1.2; P=0.16, heterogeneity P=0.01). Among these patients, the risk ratio was 0.7 (95% CI: 0.6 to 0.8, P<0.001; heterogeneity P>0.20) for fatal MI, 0.7 (95% CI: 0.6 to 0.9, P<0.01; heterogeneity P>0.20) for sudden death (N=5 trials) and 0.8 (95% CI: 0.7 to 0.9, P<0.001; heterogeneity P>0.20) for overall death.

He et al, 2004 (positive quality) This was a meta-analysis of cohort studies on the association between fish intake and CHD mortality. Eligible studies provided a relative risk (RR) and corresponding 95% confidence interval (CI) for CHD mortality in relation to fish consumption and the frequency of fish intake. A database was developed on the basis of 11 eligible studies and 13 cohorts, including 222,364 individuals with an average 11.8 years of follow-up. Six cohorts were from the US, six from Europe and one from China. PooledRR and 95% CI for CHD mortality were calculated by using fixed-effect and random-effect models. Linear regression analysis of the log RR weighted by the inverse of variance was performed to assess the possible dose-response relation.

Compared with those who never consumed fish or ate fish less than once per month, individuals with a higher intake of fish had lower CHD mortality. The pooled multivariate RRs for CHD mortality were 0.89 (95% CI, 0.79 to 1.01) for fish intake one to three times per month, 0.85 (95% CI, 0.76 to 0.96) for once per week, 0.77 (95% CI, 0.66 to 0.89) for two to four times per week and 0.62 (95% CI, 0.46 to 0.82) for five or more times per week. The observed inverse association existed in a dose-response manner. Each 20 g per day increase in fish intake was related to a 7% lower risk of CHD mortality (P for trend=0.03). The effects of fish consumption on CHD mortality were not appreciably modified by sex, but were more evident among those studies with a follow-up of 12 years or longer. The authors conclude that fish consumption is inversely associated with fatal CHD and mortality from CHD may be reduced by eating fish one time per week or more.

Konig et al, 2005 (positive quality) This was a quantitative analysis of the effect of fish consumption on CHD mortality and nonfatal MI. This analysis identified studies that were appropriate for development of a dose-response relationship. Studies had to satisfy quality criteria, quantify fish intake and report the precision of the relative risk estimates. Eight studies were identified (29 exposure groups). The analysis estimated that consuming small quantities of fish is associated with a 17% reduction in CHD mortality risk, with each additional serving per week associated with a further reduction in this risk of 3.9%. Small quantities of fish consumption were associated with risk reductions in non-fatal MI risk by 27%, but additional fish consumption conferred no incremental benefits.

Mozaffarian et al, 2008 (positive quality) This was a pooled analysis of both RCTs and prospective cohort studies on the effects of fish and n-3 fatty acid consumption on fatal CHD and sudden cardiac death (SCD), events that share a final common pathway of fatal ventricular arrhythmia. Randomized controlled trials and prospective cohort studies, provide concordant evidence that modest consumption of fish or fish oil (one to two servings per week of oily fish or approximately 250 mg per day of EPA+DHA) reduces risk of CHD death and SCD. Pooled analysis of prospective cohort studies and RCTs showed that the magnitude and dose-response of this effect to be 36% lower risk of CHD death comparing zero and 250mg per day of EPA+DHA consumption (P<0.001). There is little additional benefit with higher fish or fish oil intakes. Reductions in risk are even larger in observational studies utilizing tissue biomarkers of n-3 FA that more accurately measure dietary consumption. Results indicate that effects of fish or fish oil on CHD death and SCD do not vary with presence or absence of prior CHD. The authors indicate that the consistency of the evidence and the magnitude of the effects strongly support modest consumption of fish or fish oil as a first-line treatment for prevention of CHD death and SCD.

Mozaffarian and Rimm, 2006 (positive quality) This was a risk/benefit analysis including pooled and meta-analysis regarding fish consumption and health outcomes. The authors investigated

1. Intake of fish or fish oil and cardiovascular risk
2. Effects of methylmercury and fish oil on early neurodevelopment
3. Risks of Methylmercury for cardiovascular and neurologic outcomes in adults
4. Health risks of dioxins and polychlorinated biphenyls in fish, using both RCTs and prospective cohort studies.

When possible, meta-analyses were done to characterize benefits and risks most accurately. Modest consumption of fish (one to two servings per week), especially species higher in EPA and DHA, reduced risk of coronary death by 36% (95% CI, 20%-50%; P<0.001) and total mortality by 17% (95% CI, 0%-32%; P=0.046). Intake of 250mg per day of EPA and DHA was sufficient for primary prevention. Docosahexaenoic acid appears beneficial for, and low-level Methylmercury may adversely affect, early neurodevelopment in infants. Women of childbearing age and lactating women should consume two seafood servings per week, limiting intake to selected fish species that are high in EPA+DHA and low in methylmercury. Methylmercury may modestly counteract the cardiovascular benefits of EPA+DHA in fish. The authors conclude that based on the strength of the evidence and the potential magnitudes of effect, the benefits of fish intake exceed the potential risks. For women of childbearing age, benefits of modest fish intake, excepting a few selected species high in Methlymercury, also outweigh risks.

Wang et al, 2006 (positive quality) This was a systematic review that investigated the effects of n-3 FAs, consumed as fish or fish oils rich in EPA and DHA or as ALA, on CVD outcomes. Studies that were of at least one year in duration and that reported estimates of fish or n-3 FA intakes and CVD outcomes were included. Fourteen RCTs (11 fish oil supplement trials, five diet or diet advice trials) and one prospective cohort study addressed secondary prevention. One RCT assessing ALA supplementation, 25 prospective cohort studies and seven case-control studies reported on the association of n-3 FAs with primary prevention of CVD. Most cohort studies reported that fish consumption was associated with lower rates of all-cause mortality and adverse cardiac outcomes. Evidence suggests that increased consumption of n-3 FAs from fish or fish-oil supplements, but not of ALA, reduces the rates of all-cause mortality, cardiac and sudden death.

Whelton et al, 2004 (neutral quality), meta-analysis of observational studies, determined if fish consumption is associated with lower fatal and total CHD. This analysis included 19 observational studies (14 cohort and five case-control) in which there was a group that consumed fish on a regular basis and a comparison group that consumed little or no fish. With a standardized protocol and data extraction form, information on study design, sample size, participant characteristics, duration of follow-up, assessment of end points and consumption of fish was abstracted. Using a random effects model, the authors pooled data from each study. Fish consumption vs. little to no fish consumption was associated with a RR of 0.83 (95% CI, 0.76-0.90; P<0.005) for fatal CHD and a RR of 0.86 (95% CI, 0.81-0.92; P<0.005) for total CHD. The results indicate that fish consumption is associated with a significantly lower risk of fatal and total CHD.

Primary Articles

Albert et al, 2002 (neutral quality) prospective case control study, assessed whether blood levels of long-chain n-3 FA were associated with reduced risk of sudden death in 94 male physicians with no history of CVD as compared to 184 case controls matched for age and smoking status. Baseline blood level of long-chain n-3 FA was significantly correlated with fish intake at 12 months (R2=0.24, P=0.001). The mean level of total long-chain n-3 FA was significantly lower among the men who died suddenly than among the controls (4.82±1.31 vs. 5.24%±1.32% of total fatty acids, P=0.01). Baseline blood levels of long-chain n-3 FA were inversely related to the risk of sudden death both before adjustment for age and smoking status (P=0.004) and after such adjustment (P=0.007). As compared with men whose blood levels of long-chain n-3 FA were in the lowest quartile (3.58% total fatty acids), the adjusted risk of sudden death was significantly lower among men with levels in the third quartile (AHR, 0.28; 95% CI 0.09-0.87) and the fourth quartile (6.87% total fatty acids) (AHR, 0.19; 95% CI: 0.05-0.71).

Brouwer et al, 2006 (positive quality) This was a prospective cohort study that examined the association between consumption of very long-chain n-3 FA EPA plus DHA from fish and risk of incident atrial fibrillation using data from the Rotterdam Study, involving 5,184 subjects free from atrial fibrillation and whose dietary intake data were available. Dietary intake was assessed using a semi-quantitative food-frequency questionnaire (FFQ) and incidence of atrial fibrillation was continuously monitored during follow-up. Three hundred twelve subjects developed atrial fibrillation. Intake of EPA and DHA in the third textile compared with first was not associated with risk of atrial fibrillation (RR 1.18, 95% CI 0.88-1.57). No association was observed with intake of >20g per day fish compared with no fish intake (RR: 1.17, 95% CI 0.87-1.57). After a mean follow-up period of 6.4±1.6 years, intake of EPA and DHA and fish consumption were not associated with a reduced risk of atrial fibrillation. The findings do not support the anti-arrhythmic effect of n-3 FAs.

Erkkila et al, 2003 (positive-quality) prospective cohort study, in 415 free-living adults with established coronary artery disease (CAD), found that proportions of ALA, EPA and DHA in serum cholesterylesters were associated with a reduction in the risk of death (P for trend=0.063, 0.056 and 0.026, respectively). The associations of n-3 FAs with combined fatal and non-fatal cardiovascular events were NS. Compared with no consumption, consumption of fish tended to be associated with a lower risk of death [1g to 57g per day, RR=0.50 (0.20, 1.28); >57g per day, RR=0.37 (0.14, 1.00); P for trend=0.059].

Erkkila et al, 2004 (positive-quality) prospective cohort study, examined the association between fish intake and the progression of coronary artery atherosclerosis over a three-year period in 229 postmenopausal women. Women who ate two or more servings of fish per week had significantly fewer new lesions (P=0.03). Women who ate at least one serving of tuna or dark fish per week had a smaller change in minimum coronary artery diameter (P=0.02). Among the 42% of women who were diabetic, compared with lower fish intakes, consumption of at least two servings of fish or at least one serving of tuna or dark fish per week was associated with smaller increases in the percentage of stenosis after adjustments for age, CVD risk factors and dietary intakes of fatty acids, cholesterol, fiber and alcohol. This relationship was only significant in non-diabetic women when adjustment was made for dietary factors, which suggests an independent effect of tuna and dark fish (P=0.02). In the same cohort of patients, Erkkila et al, 2006, reported women with plasma phospholipids (PL) DHA levels above the median, compared with below, exhibited less atherosclerosis progression, as expressed by decline in minimum coronary artery diameter (-0.04±0.02 and -0.10±0.02mm, respectively; P=0.007) or increase in percentage stenosis (1.34±0.76% and 3.75±0.74%, respectively; P=0.006) and had fewer new lesions [2.0% (0.5% to 3.5%) of measured segments (95% CI) and 4.2% (2.8% to 5.6%), respectively; P=0.009] after adjustments for cardiovascular risk factors.

Folsom and Demissie, 2004 (neutral quality) prospective cohort study, assessed the effect of fish or marine n-3 FA intake on CVD and CHD mortality over a 10-year period in 41,836 postmenopausal women aged 55-69 years, initially free of heart disease and cancer (4,653 deaths over 442,965 person-years). A FFQ was used to determine if intake may decrease risk of total and CHD death. Among women initially free of heart disease and cancer there was an inverse age- and energy-adjusted association between total mortality and fish intake, with a RR of 0.82 (95% CI: 0.74, 0.91) for the highest vs. lowest quintile. Age- and energy-adjusted associations also were inverse (P for trend<0.05), although not entirely monotonic, for cardiovascular, CHD and cancer mortality. Adjustment for multiple other risk factors attenuated all associations to statistically NS levels. Estimated marine n-3 fatty acid intake also was not associated with total or cause-specific mortality. In comparison, plant-derived ALA was inversely associated with mortality after multivariable adjustment. There was no independent association of fish intake with CHD or stroke mortality.

Frost and Vestergaard, 2005 (positive quality) This was a prospective cohort study that examined the association between consumption of n-3 FAs from fish and risk of atrial fibrillation or flutter in a prospective cohort study of 47,949 participants (mean age: 56 years) in the Danish Diet, Cancer, and Health Study, using a

detailed semi-quantitative FFQ and risk of atrial fibrillation or flutter. The subjects were followed-up in the Danish National Registry of Patients for the occurrence of atrial fibrillation or flutter and in the Danish Civil Registration System (vital status and emigration). The consumption of n-3 FAs from fish was analyzed as sex-specific quintiles with the use of Cox proportional hazards models. During the mean follow-up of 5.7 years atrial fibrillation or flutter developed in 556 subjects (374 men and 182 women). When the lowest quintile of n-3 FAs consumed from fish was used as a reference, the unadjusted hazard rate ratios (HR) in quintiles two, three, four and five were 0.93, 1.11, 1.10, and 1.44, respectively (P for trend=0.001). The corresponding adjusted HR were 0.86, 1.08, 1.01, and 1.34 (P for trend=0.006). Inclusion of information on the frequency of fatty fish consumption did not alter these associations. Consumption of n-3 FAs from fish was not associated with a reduction in risk of atrial fibrillation or flutter.

Iso et al, 2006 (positive quality) prospective cohort study, examined the association between high intake of fish and n-3 PUFA and the risk of CHD in 41,578 Japanese men and women aged 40 to 59 years, free of prior diagnosis of CVD and cancer and who completed a FFQ and were followed up from 1990-1992 to 2001. After 477,325 person-years of follow-up, 258 incident cases of CHD (198 definite and 23 probable MI and 37 SCD) were documented, comprising 196 non-fatal and 62 fatal coronary events. Strong inverse associations existed between dietary intake of n-3 FAs and risk of definite MI (HR=0.35 [0.18 to 0.66]) and nonfatal coronary events [hazard ratios (HR)=0.33 (0.17 to 0.63)]. For men, the multivariable HR (95% CI) in the highest vs. lowest quintiles of n-3 PUFAs were 0.54 (0.30 to 0.96), for total CHD 0.41 (0.21 to 0.80) for total MI, 0.35 (0.17 to 0.73) for definite MI, 0.33 (0.16 to 0.69) for non-fatal coronary events, 0.99 (0.27 to 3.62) for SCD and 1.06 (0.37 to 2.99) for fatal coronary events. The multivariable HRs and 95% CI in the highest (eight times per week, or median intake=180g per day) vs. lowest (once a week, or median intake=23g per day) quintiles of fish intake were 0.63 (0.38 to 1.04) for total CHD, 0.44 (0.24 to 0.81) for definite MI and 1.14 (0.36 to 3.63) for SCD. The reduced risk was primarily observed for nonfatal coronary events (HR=0.43 [0.23 to 0.81]), but not for fatal coronary events (HR=1.08 [0.42 to 2.76]). Authors conclude that compared with a modest fish intake of once a week or 20g per day, a higher intake was associated with substantially reduced risk of CHD, primarily non-fatal cardiac events, among middle-aged persons.

Järvinen et al, 2006 (positive quality) prospective cohort study, investigating the relationship between consumption of fish and long-chain n-3 FA and the risk of coronary heart mortality in 2,775 men and 2,445 women aged from 30 to 79 years who were free of CHD and had participated in a health examination survey from 1967 to 1972. In total, 335 men and 163 women died of CHD during a follow-up until the end of 1992. A dietary history interview method provided data on habitual consumption of fish and other foods over the preceding year at baseline. The intakes of long-chain n-3 FAs were calculated on the basis of food composition values of Finnish foods. Higher consumption of fish was associated with a decreased risk of CHD among women, whereas NS association was seen among men. The RR between the highest and the lowest quintile for fish consumption was 1.00 (95% CI 0.70, 1.43; P for trend 0.83) for men and 0.59 (95 % CI 0.36, 0.99; P for trend 0.02) for women in analysis adjusting for age, energy intake, geographical area, body mass index (BMI), serum cholesterol, BP, smoking, occupation and diabetes; however, after adjustment for dietary confounders this association was no longer significant. The intake of n-3 FAs was NS associated with the risk of CHD in either men or women. In conclusion, our results for women are in line with the suggested protective effect of fish consumption against CHD but a similar association was not, however, found in men.

Lankinen et al, 2009 (neutral quality) RCT, examined how dietary fatty fish or lean fish affect serum lipidemic profiles in subjects with CHD. The study included 33 subjects with MI or unstable ischemic attack in an eight-week parallel controlled intervention trial. The subjects were randomized to either fatty fish (N=11), lean fish (N=12) or control (N=10) groups. Subjects in the fish groups had four fish meals per week and subjects in the control group consumed lean beef, pork and chicken. Lipidomics analyses were performed using ultra performance liquid chromatography coupled to electrospray ionization mass spectrometry and gas chromatography. Multiple bioactive lipid species, including ceramides, lysophosphatidylcholines and diacylglycerols, decreased significantly in the fatty fish group, whereas in the lean fish group cholesterol esters and specific long-chain triacylglycerol increased significantly. The authors conclude that the eight-week consumption of fatty fish decreased lipids which are potential mediators of lipid-induced insulin resistance and inflammation and may be related to the protective effects of fatty fish on the progression of atherosclerosis or insulin resistance.

Lara et al, 2007 (positive quality) RCT, examined the effect of fish intake in 48 non-obese, healthy adults aged 20-55, who consumed 125g per day of salmon for a four-week period followed by a four-week period with no-fish (41 completers). Blood pressure, anthropometric, body composition, blood lipids and dietary information were assessed. Compared to no-fish, eating salmon significantly decreased systolic BP (SBP) diastolic BP (DBP) and mean arterial pressure (MAP) by 4%, TG by 15%, LDL-C by 7% and significantly increased HDL-C by 5% ($P<0.05$). The authors state that the changes in BP and lipids alone with salmon intake predict approximately 25% reduction in CHD risk based on the PROCAM risk calculator. The authors conclude that daily consumption of salmon improves risk predictors of CHD in non-obese subjects.

Lemaitre et al, 2003 (positive quality) case-control study, (N=179 pairs) nested in the Cardiovascular Health Study cohort, found free-living older adults (over age 65), after adjustment for risk factors, a higher concentration of combined plasma DHA and EPA was associated with a lower risk of fatal ischemic heart disease (IHD). Based on data from 54 cases of fatal IHD, 125 cases of non-fatal MI and 179 matched controls, for a one-SD increase in plasma phospholipids DHA and EPA, there was an associated 70% lower risk of fatal IHD (OR: 0.30; 95% CI: 0.12, 0.76; P=0.01) and for a one-SD increase in ALA, there was an associated 50% lower risk of fatal IHD (OR: 0.48; 95% CI: 0.24, 0.96; P=0.04). The first controlled for coronary risk factors, updated prior report of CVD, alcohol intake, aspirin, vitamin supplements and postmenopausal hormone use. The second included the covariates in model one and additionally controlled for intake of other fatty acids that resulted in a change of more than 10% in the parameter estimate for ALA intake.

Lindqvist et al, 2009 (neutral quality) This was an RCT to evaluate the effects of a diet rich in specified, pre-made herring meals on CVD risk factors in healthy over weight men. The design was a cross-over intervention on the effect of a six week herring diet compared with a reference diet on CVD risk factors. Thirty-five healthy, butoverweight, men (mean BMI 28.3kg/m^2) were randomized to a six-week herring diet (150g baked herring fillets per day, five days per week) or a reference diet (150g baked lean pork and chicken fillets per day, five days per week) with a 12-week washout period. Plasma TC, triacylglycerols (TAG), HDL, HDL2, HDL3, LDL, C-reactive protein (CRP), IL-6, IL-18, intercellular adhesion molecule-1, oxidized LDL, oxygen radical absorbance capacity using perchloric acid (ORACPCA), whole-blood fatty acids, bleeding time and BP were measured at the beginning and end of each dietary period. High-density lipoprotein was significantly higher after the herring diet period compared with after the reference diet period: 1.04 vs. 0.99 mmol per L. Triacylglycerols decreased after both diets, with NS difference between the two diets. ORACPCA values did not indicate lower concentrations of non-protein plasma antioxidants and oxidized LDL was not higher after the herring diet than after the reference diet. The authors conclude that a six week herring-rich diet significantly raised HDL. No adverse effects on in vivo oxidation or serum antioxidants were found after herring intake.

Mozaffarian et al, 2005 (positive quality), prospective study, examined the interplay between intermediate and long chain n-3 FA and n-6 FA intake on the incidence of CHD in 45,722 male health professionals. Dietary n-3 FA and n-6 FA intake were assessed by administration of a self-administered validated FFQ at multiple time points and development of CHD assessed by a biennial health history questionnaire. Over 14 years of follow-up, participants experienced 218 sudden deaths, 1,521 non-fatal MIs, and 2,306 total CHD events (combined sudden death, other CHD deaths and non-fatal MI). Relative risk of non-fatal MI was lower in those with high intakes of ALA (RR=0.58; 95% CI 0.23 to 0.75). This effect of ALA on total CHD and non-fatal MI occurred mostly among men with low intakes of EPA plus DHA. Long-chain and intermediate-chain n-3 FA intakes were associated with lower CHD risk, without modification by n-6 FA intake when adjusted for age; BMI; smoking; physical activity; history of diabetes, hypertension (HTN) or hypercholesterolemia; aspirin use; alcohol use; and intake of protein, SFA, dietary fiber, MUFA, TFA, total calories and ALA. High intake of EPA plus DHA (more than 250mg per day or equivalent to one or two fish meals per week) compared to low intake (less than 250mg per day) was associated with a 35% lower risk of sudden death (RR=0.65; 95% CI; 0.47 to 0.88). High intake of EPA plus DHA was associated with reduced sudden death regardless of ALA level.

Mozaffarian et al, 2004 (positive quality) This was a prospective cohort study of 4,815 adults at least 65 years old, with dietary intake assessed at baseline in 1989 and 1990. Consumption of tuna and other broiled or baked fish correlated with plasma phospholipids long-chain n-3 FAs, whereas consumption of fried fish or fish sandwiches (fish burgers) did not. Atrial fibrillation (AF) incidence was prospectively ascertained on the basis of hospital discharge records and annual electrocardiograms. During 12-year follow-up, 980 cases of incident AF were diagnosed. In multivariate analyses, consumption of tuna or other broiled or baked fish was inversely associated with incidence of AF, with 28% lower risk with intake one to four times per week (HR=0.72 95% CI=0.58 to 0.91, P=0.005), and 31% lower risk with intake at least five times per week (HR=0.69, 95% CI=0.52 to 0.91, P=0.008), compared with less than one time per month (P trend=0.004). Results were not different after adjustment for preceding MI or congestive heart failure (CHF). In similar analyses, fried fish/fish sandwich consumption was not associated with lower risk of AF. The authors conclude that among elderly adults, consumption of tuna or other broiled or baked fish, but not fried fish or fish sandwiches, is associated with lower incidence of AF.

Panagiotakos et al, 2007 (neutral quality) This was a prospective cohort study of 542 subjects (men: 234; women: 308), from Cyprus (aged 65 to 100 years). Dietary habits (including fish consumption) were assessed with FFQs. Sixty-one percent of the participants reported that they had consumed fish approximately once

a week (mean intake: 1.9±1.2 servings per week) for a mean period of 30 years. After adjusting for confounders, fish intake was inversely associated with SBP (P=0.026), fasting glucose (P<0.001), total serum cholesterol (P=0.012) and TG levels (P=0.024). Multinomial logistic regression revealed that a decrease of 100g per week in fish intake was associated with a 19% (95%CI: 1-41) higher likelihood of having one additional cardiovascular risk factor (i.e., HTN, hypercholesterolemia, diabetes, obesity). The authors conclude that long-term fish intake is associated with reduced levels of the most common CVD risk markers in a cohort of elderly people.

Seierstad et al, 2005 (positive quality) This was a double-blinded RCT. Sixty patients with CHD were randomly allocated to three groups consuming approximately 700g per week for six weeks of differently fed Atlantic salmon: 100% fish oil (FO), 100% rapeseed oil (RO) or 50% of each (FO/RO), resulting in fillets with high, intermediate and low levels of long-chain n-3 PUFA (EPA+DHA). The serum fatty acid profiles of subjects after the intervention reflected those of the corresponding salmon fillets and the respective salmon feeds. Significant differences between the groups were obtained, especially for the levels of total n-3 PUFAs and the n-3/n-6 FA ratio, which were markedly increased in the FO group in contrast to the two other groups (P<0.02 for all). In response to these changes there were significant reductions of serum TG and inflammation markers including vascular cell adhesion molecule-1 and interleukin-6 in subjects receiving the FO diet when compared with the two other groups (P<0.05 for all). The authors conclude that the FA differences in salmon fillets, in particular those very high in EPA+DHA result in favorable changes in subjects with CHD when compared with ingestion of fillets with intermediate and low levels of marine n-3 PUFAs.

Streppel et al, 2008 (neutral quality) This was a prospective cohort study conducted in the Netherlands. The study investigated the relationship between fish consumption or EPA + DHA intake from fish, and (sudden) coronary death (SCD) in the Zutphen Study, a cohort of 1,373 men born between 1900 and 1920, and examined repeatedly between 1960 and 2000. Hazard ratios (HR) were obtained from time-dependent Cox regression models. The associations between long-term fish consumption, EPA+DHA intake, and SCD were stronger than those of recent consumption. Long-term fish consumption was inversely associated (borderline significant) with CHD death; however, the strength of the association decreased from age 50 [HR: 0.32 (95% CI: 0.13-0.80)] until age 80 [HR: 1.34 (0.58-3.12)]. For men with a daily EPA+DHA intake from fish below 250mg compared with no intake, CHD death risk was reduced to the same extent as for men with a daily intake above 250mg (P-value for trend=0.27). Long-term fatty-fish consumption lowered the risk of SCD [HR: 0.46 (0.27-0.78)]. The authors concluded that the strength of the association between long-term fish consumption and CHD death decreased with increasing age. Fatty-fish consumption lowered sudden coronary death risk with no clear dose-response relationship between EPA+DHA intake and SCD.

Turunen et al, 2008 (neutral quality) This was a cohort study conducted in Finland, assessed the cause-specific mortality of professional fishermen and their wives. Fish consumption was measured using a self-administered semi-quantitative FFQ, and fasting blood samples were also taken. 4,487 fishermen and their wives were followed from 1980 to 2005 and mortality rates were recorded. The average fish consumption and serum concentrations of fish-derived fatty acids and environmental contaminants were higher among the fishermen and their wives than among the general population from the same region. Fishermen and their wives exhibited a lower mortality for all causes [standard mortality ratio (SMR)=0.78, 95% CI: 0.73-0.82 for fishermen, SMR=0.84, 95% CI: 0.76-0.93 for wives] as well as IHD) SMR=0.73, 95% CI: 0.65-0.81 for fishermen, SMR=0.65, 95% CI=0.50-0.83 for wives) than the general population. Mortality from cerebrovascular diseases and malignant neoplasm was decreased among fishermen (SMR=0.67, 95% CI: 0.52-0.85, SMR=0.90, 95% CI: 0.80-1.01, respectively, for fishermen only), but not their wives.

Virtanen et al, 2009 (positive quality) prospective population-based cohort study, examined the relationship between serum concentrations of long-chain n-3 PUFA, EPA, docosapentaenoic acid (DPA) and DHA, which also serve as a marker of fish or fish oil consumption, and risk of atrial fibrillation (AF) in middle-aged or older men, 42-60 years old and free of AF at baseline (1984-1989) in Eastern Finland. During 17.7 years of follow-up, 240 men from the total cohort of 2,174 men experienced an AF event that required hospitalization. Men in the highest quartile of serum EPA+DPA+DHA had a 35% lower risk of AF compared with men in the lowest quartile. Of the individual fatty acids, only serum DHA was associated with the risk, with a 38% lower risk in the highest quartile. No association with the risk was found with serum intermediate chain-length n-3 PUFA ALA, not even when the serum EPA+DPA+DHA concentration was low. Authors conclude that long-chain n-3 PUFAs, and especially DHA, may be effective in reducing the risk of AF in men.

Virtanen et al, 2008 (positive quality) prospective cohort study conducted in the US. The study investigated the associations of fish and n-3 fatty acid consumption with risk of total major chronic disease (CVD, cancer, and death) and to determine whether a high n-6 intake modifies the associations. Lifestyle and other risk factors were assessed every two years and diet every four years (using a validated FFQ) in 40,230 US male health professionals aged 40-75 years and free of major chronic disease at baseline in 1986. During 18 years of follow-up, 9,715 major chronic disease events occurred, including 3,639 CVD events, 4,690 cancers and 1,386 deaths from other causes. After multivariable adjustment, neither fish nor dietary n-3 fatty acid consumption was significantly associated with risk of total major chronic disease. Compared with fish consumption of less than one serving per month, intake of one serving per week and of two to four servings per week was associated with a lower risk of total CVD of approximately 15%. The RR in the highest quintile was 0.97 (95% CI: 0.90, 1.04; P for trend=0.37) for major chronic disease, and 0.97 (95% CI: 0.87, 1.09; P for trend=0.93) for CVD after multivariate adjustments. Fish or EPA+DHA consumption and n-6 FA intake were not strongly correlated (r= -0.09 and -0.11, respectively). No significant effect modification by n-6 FA intake was seen (P for interactions>0.10) based on multivariate-adjusted RRs for major chronic disease, total CVD and total cancer according to both fish and n-6 FA intakes. Higher or lower n-6 FA intake did not significantly modify the results (P for interaction>0.10). The authors concluded that modest fish consumption was associated with a lower risk of total CVD, consistent with cardiac mortality benefits and that intake EPA+DHA and fish was not associated with the overall incidence of major chronic disease in generally healthy men.

Yamagishi et al, 2008 (neutral quality) This was a prospective cohort study conducted in a nationwide community-based cohort of 57,972 Japanese men and women who were part of the JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk) Study. The study investigated the hypothesis that fish or n-3 PUFA intake is inversely associated with risks of mortality from IHD, cardiac arrest, heart failure, stroke and total CVD. Dietary intakes of fish and n-3 PUFA were determined by FFQ and participants were followed up for 12.7 years. Hazard ratios (HR) and 95% CI were calculated according to quintiles of fish or n-3 PUFA intake. The study documented 419 deaths due to IHD (including 329 MI), 107 due to cardiac arrest, 307 due to heart failure and 972 due to stroke (including 223 intraparenchymal hemorrhages, 153 subarachnoid hemorrhages, and 319 ischemic strokes); there were 2,045 total cardiovascular deaths and 7,008 total deaths. Inverse associations of fish and n-3 PUFA intakes with risks of mortality from heart failure (multivariable HR [95% CI] for highest vs. lowest quintiles=0.76 [0.53 to 1.09] for fish and 0.58 [0.36 to 0.93] for n-3 PUFA) were observed. Associations with IHD or MI were relatively weak and statistically NS after adjustment for potential risk factors. Neither fish nor n-3 PUFA dietary intake was associated with mortality from total stroke, its subtypes or cardiac arrest. For mortality from total CVD, intakes of fish and n-3 PUFA were associated with 18% to 19% lower risk. The authors conclude that an inverse association between fish and n-3 PUFA dietary intakes and cardiovascular mortality, especially for heart failure, suggesting a protective effect of fish intake on CVD.

View table in new window

Author, Year, Study Design, Class, Rating	Study Description/Duration	Study Population/ Location	Intervention Protocol/Exposure levels	Significant Results	Limitations
Albert CM, Campos H et al, 2002 Study Design: Prospective nested case control Class: C Rating:		Male Physicians' Health Study. Age: 40-84 years old in 1982. Healthy men: • N=94 in whom sudden death occurred as first symptom of CVD. • N=184 controls matched for age and	n-3 fatty acids and CVD. **Baseline**: Questionnaire on health status/CVD risk factors, blood samples. **12 months**: Dietary intake of fish ascertained in shortened FFQ. **Six months**: CVD	Mean level of total long-chain n-3 FAs significantly ↓ among men who died suddenly than among controls. Baseline blood levels of long-chain n-3 FAs were inversely related to risk of sudden death both before adjustment for age and smoking status and	Analyses on a single base-line measurement and may not accurately reflect levels of long-chain n-3 FAs over long periods. Use of whole blood combines two different pools of long-chain n-3 FAs, the plasma and the stored red-cell pools.

		smoking status Location: United States.	information updated. **One year and annually for 17 years**: CVD information updated.	after adjustment.	Authors tried to control these confounders.
Brouwer IA, Heeringa J et al, 2006 Study Design: Prospective cohort study. Class: B Rating:	Mean follow-up: 6.4 years (±1.6 years).	N=5,184 subjects (2,105 men and 3,079 women). Mean age: 67.4±7.7 years. Location: The Netherlands	**EPA+DHA and Atrial fibrillation** Data on health status, medical history, smoking, BMI and BP obtained at baseline. Dietary assessment was obtained using a self-administered FFQ and interview with a trained dietitian. Outcome measure: Atrial fibrillation.	Intake of EPA+DHA and fish consumption were not associated with a ↓ risk of atrial fibrillation.	None.
Bucher HC, Hengstler P et al 2002 Study Design: Meta-analysis. Class: M Rating:		N=7,951 subjects with intake of n-3 PUFA and 7,855 control subjects. 11 RCTs were included in which n-3 PUFA from diet or supplement with placebo in patients with existing CHD as evidenced by previous MI or angina for six months or more. Excluded studies had patients with coronary bypass or transplantation surgery.	**Dietary and non-dietary n-3 PUFA and CHD** In trials of supplementation with n-3 PUFAs, the dose for EPA varied from 0.3 to 6.0g, whereas the dose for DHA ranged from 0.6 to 3.7g. Mean follow up: 20 months (range six to 46 months).	For non-fatal MI, the risk ratio in two trials of dietary intervention compared with controls was 0.8 (95% CI: 0.5 to 1.2; P=0.16, heterogeneity P=0.01). Among these subjects, the risk ratio was 0.7 (95% CI: 0.6 to 0.8, P<0.001; heterogeneity P>0.20) for fatal MI, 0.7 (95% CI: 0.6 to 0.9, P<0.01; heterogeneity P>0.20) for sudden death (N=5 trials) and 0.8 (95% CI: 0.7 to 0.9, P<0.001; heterogeneity P>0.20) for overall death. Supplementation with n-3 PUFA ↓ mortality due to MI (RR 0.7 with 95% CI 0.6-0.8; P<0.001) and sudden death (RR 0.7; 95% CI 0.6-0.9; P<0.01) in subjects with CHD.	No description of fish intake was provided.
Erkkila AT, Lehto S et al, 2003 Study Design: Cohort Class: B Rating:		N=415 free living adults with established CAD. Location: Finland.	**Fish intake and CVD events** Three categories: • No fish (0g per day) • Above the median intake (57g per day) • Below median intake.	Proportions of ALA, EPA and DHA in serum cholesterylesters associated with a ↓ in the risk of death (P for trend=0.063, 0.056 and 0.026, respectively). Associations of n-3 FA with combined fatal and non-fatal CV events NS. Compared with no consumption, intake of fish tended to be associated with ↓ risk of death [1g-57g per day, RR=0.50 (0.20, 1.28); >57g per day, RR=0.37 (0.14, 1.00); P for trend=0.059].	Type of fish consumed not reported.
Erkkilä, Lichtenstein etal 2004 Study Design: Cohort study. Class: B	Three-year follow-up coronary angiography as part of a RCT of hormone replacement therapy (HRT).	N=229 postmenopausal women with coronary stenosis. 30% or greater of the luminal diameter. Age: ~65 years (~ 85%).	**n-3 intake and progression of CAD** FFQ: Frequency of fish consumption by summing the frequency of intake of (per serving):	Intake of ≥two servings of fish per week had significantly fewer new lesions (P=0.03). Intake of ≥one serving of tuna or dark fish per week had a smaller Δ in minimum coronary artery.	Authors note: Three-year follow-up may have been too short to full address association between CAD progression and all n-3 FAs.

Rating:		12% African American. Location: United States.	• Tuna (84g to 112g) • Dark fish (84g to 140g) • Other fish (84g to 140g). Tuna and dark fish intake calculated by summing the two intakes alone.	Among diabetics (42%): Δ in minimum coronary artery diameter was significantly smaller in women who eat ≥two servings of fish per week (P=0.02). Mean baseline percentage stenosis also greater, with a smaller Δ (P=<0.001).	
Erkkilä, Matthan et al, 2006 Study Design: Cohort Class: B Rating:	Follow-up: Three years.	N=228 women. Postmenopausal with established CAD. Location: United States.	N-3 intake and CAD progression. Measurements of coronary artery diameter. Percent stenosis and new lesion formation. Assessment of plasma n3 FA: ALA, EPA and DHA with habitual fish intake with no supplements. Median values are: In PL: ALA, 0.17; EPA, 0.49; DHA, 2.50.	↑ levels of DHA in plasma PL and TG significantly associated with the ↓ progression of coronary atherosclerosis.	Authors note: Three-year follow-up may have been too short to fully address association between CAD progression and all n-3 FAs.
Folsom and Demissie, 2004 Study Design: Cohort study. Class: B Rating:		N=41,836 postmenopausal women without initial history of heart disease from Iowa. Location: United States.	Fish or marine omega-3 FA intake and cause of death (CVD or CHD). Baseline dietary intake assessed in 1986 using a FFQ with four fish and seafood questions. Mean respective intakes of EPA, DHA and total marine N-3 FAs were 53mg, 135mg and 188mg per day. The mean intake of ALA was 1.09g per day.	No independent association of fish intake with CVD, CHD or stroke mortality.	None.
Frost L and Vestergaard P, 2005 Study Design: Retrospective cohort study Class: B Rating:	Mean follow-up: 5.7 years.	N=47,949 (22,528 men; 25,421 women). Mean age: 56 years 374 men and 182 women had incident of atrial fibrillation or flutter. Location: Denmark.	Marine n-3 FA and atrial fibrillation Subjects completed a FFQ and a questionnaire about fish consumption and 3,818 subjects completed a 24-hour recall. Mean consumption of marine n-3 FA in the top quintile was >1g per day in men and women. Correlation coefficient between reported dietary intake and relative fat tissue composition of EPA and DHA was 0.47 and 0.41, respectively.	During a follow-up of 5.7 years (mean) atrial fibrillation or flutter had developed in 556 subjects Consumption of n-3 FAs from fish was not associated with a reduction in risk of these events.	None.
He K, Song Y et al, 2004 Study Design: Meta-analysis or Systematic Review Class: M	Follow-up: 6 to 30 years (11.8 years average).	N=222,364 participants (only males in eight cohorts). Range (N)=852-84,688 participants. 13 cohorts from 11 independent studies:	Fish intake and CHD. Self-administered FFQ. Amount of fish intake=frequency of intake (servings per day) x portion size (g per serving)	Fish intake one time per week: Significantly ↓ CHD mortality rates (pooled multivariate RR, 0.85; 95% CI, 0.76 to 0.96) vs. Never consumed fish or ate fish Fish intake ≥five times per week: Percent CHD	Dietary assessment, number of exposure categories and the reference group varied across individual studies Results likely affected by misclassification of fish intake

Rating:		• United States: Six • Europe: Six • China: One.	Five categories of fish intake intervals: • Never or • One to three times per month • One time per week • Two to four times per week • ≥ five times per week. Five studies provided data on non-fatal MI.	mortality by 38% (RR, 0.62; 95% CI, 0.46 to 0.82). Dose relation: For each 20g per day number in fish intake, the pooled RR estimated to be 0.93 (95% CI, 0.87 to 0.99; P for trend=0.03. Non-fatal MI: Pooled RR across five categories of fish intake: 1.0; 0.88 (95% CI, 0.70 to 1.10); 0.95 (95% CI, 0.75 to 1.22); 0.86 (95% CI, 0.67 to 1.09) and 0.79 (95% CI, 0.64 to 0.99; P for trend=0.40).	
Iso H, Kobayashi M et al, 2006 Study Design: Prospective cohort study Class: B Rating:	Follow-up: 11 years.	N=41,578 (19,985 men and 21,593 women) free from CHD. Age: 40-52 years. Location: Japan.	↑ intake of fish and n-3 FA and the risk of CHD. Two FFQ assessed fish intake; how often in past month (1990 FFQ) or year (1995 FFQ) subject consumed fish. A portion size for each food was specified in the 1995 FFQ, but not in the 1990 FFQ. Researchers multiply frequency score of each food with each portion size. For intake of n-3 FAs, researchers assigned grams per serving fish in 1990 and specific values for each of the fish and fish products in 1995. Death certificates and medical records reviewed to assess coronary events.	HR (95% CIs) for energy-adjusted intake of n-3 FAs, in the highest (eight times per week, median intake of 180g per day) vs. lowest (one time per week or median intake of 23g per day) quintiles of intake were: 0.61 (0.38 to 0.97) for total CHD, 0.44 (0.26 to 0.75) for MI, 0.33 (0.18 to 0.61) for definite MI, 0.32 (0.17 to 0.61) for non-fatal coronary events, 2.52 (0.75 to 8.48) for SCD and 1.92 (0.79 to 4.66) for fatal coronary events. When adjusted for age, gender, smoking, alcohol intake, BMI, histories of HTN and DM, medication use for hypercholesterolemia, education level, sports at leisure time, quintiles of dietary intake of fruits, vegetables, SFA, MUFA, n-6 PUFA, cholesterol, total energy and Public Health Clinic.	Participants who had a ↑ intake of fish and n-3 PUFA were at lower risk of CHD because of other health habits and behaviors. Measurement errors in assessing nutrient intake were inevitable. Since the baseline FFQ underestimated fish intake by one third, whereas the five-year follow-up questionnaire did so only by 16% in men and 1% in women.
Jarvinen R, Knekt P et al, 2006 Study Design: Prospective Cohort Study Class: B Rating:		N=2,775 men; 2,445 women; free from CHD. Age: 30-79 years. Location: Finland.	Consumption of fish and long-chain n-3 FA and coronary heart mortality. Dietary history interview method provided data on consumption of fish and other foods over the preceding year at baseline. Intakes of long-chain n-3 FA were calculated on the basis of food composition values of Finnish foods.	↑ consumption of fish associated with ↓ risk of CHD among women. NS association was seen among men. RR between highest and lowest quintile for fish consumption was 1.00 (95 % CI 0.70, 1.43; P for trend 0.83) for men and 0.59 (95 % CI 0.36, 0.99; P for trend 0.02) for women. Analysis adjusted for age, energy, geographical area, BMI, serum cholesterol, BP, smoking, occupation and diabetes. However, after adjustment for dietary confounders this association was NS. Intake of n-3 FAs NS associated with risk of CHD	None.

				in men or women.	
Konig A, Bouzan C et al, 2005 Study Design: Meta-analysis or Systematic Review Class: M Rating:	Quantitative risk analysis.	Eight studies identified, including 29 exposure groups. Updated Wang et al, 2002. Results combined into a single data set. Combines the RR values from included studies, weighted by their statistical precision and regressed against fish consumption (servings per week).	**Analysis of Fish Consumption and CHD Mortality** Fish consumption assessed by conversion of consumption rates expressed as ranges (e.g., one to three fish servings per month) into point estimates expressed as average fish consumption servings per week.	Estimated consumption of small quantities of fish (~one serving per week) was associated with a 17% ↓ in CHD mortality risk; each additional serving per week associated with a further ↓ in risk of 3.9%. Small quantities of fish were associated with a ↓ risk of non-fatal MI by 27%, but additional fish consumption conferred no further benefit.	Detail characteristics of study populations in pooled analysis not provided. Insufficient number of RCTs included to make meaningful inferences and not clear how Δ in the type of fish consumed affects risk.
Lankinen et al 2009 Study Design: Randomized Controlled Trial Class: A Rating:	Duration: 8 weeks.	N=33 subjects. Age: <70 years. Subjects with prior MI or unstable ischemic attack. Location: Finland. Trial Registration: ClinicalTrials. gov NCT00720655.	**Fatty fish and blood lipids** Subjects randomized to fatty fish (N=11), lean fish (N=12) or control (N=10) groups. Subjects in oily fish groups had four fish meals per week [salmon, trout, herring, etc] and in the lean fish group [pike, perch, saithe, cod]; subjects in control group consumed lean beef, pork and chicken. Lipidomic approach: measured multiple bioactive lipids, including ceramides, lyso-phosphatidylcholines and diacylglycerols.	Eight-week consumption of fatty fish ↓ lipids that are mediators of insulin resistance and inflammation. In fatty fish group, ceramides, lysophosphatidylcholines and diacylglycerols were significantly ↓. In lean fish group, cholesterol esters and long chain FA TG ↑ significantly. Concluded that fatty fish may have protective effects on atherosclerosis progression or insulin resistance.	Subjects had to use beta-blockers. Subjects all on statins.
Lara JJ, Economou M et al, 2007 Study Design: Randomized Controlled Trial Class: A Rating:	Eight weeks (four plus four weeks with or without fish).	48 non-obese, healthy adults. Age: 20-55 years. Attrition: 8.5%	**Fish Intake and lipid profile:** Consumed 125g per day of salmon for four weeks. No fish for another four weeks. No washout period.	**Compared to no-fish:** Salmon intake • ↓ SBP, DBP and MAP by 4% (P<0.05) • ↓ TG by 15% (P<0.05) • ↓ LDL-C by 7% (P<0.05) • ↑ HDL-C by 5% (P<0.05).	None.
Lemaitre RN, King IB et al, 2003 Study Design: Prospective nested case-control Class: C Rating:		N=54 cases of fatal IHD; N=125 cases of non-fatal MI and 179 matched controls of free-living adults. Recruited from CV health Study Cohort (N=5,201), non-institutionalized; 1989. 687 additional African Americans. Age: >65 years. Location: United States.	**Plasma EPA+DHA and IHD** Case-control study nested in a CV health study; No intervention. Plasma phospholipids concentration of DHA, EPA and ALA taken two years before the event were used as a biomarker for intake. Fish oil supplement users excluded from study.	Traditional IHD more prevalent in cases than in controls. Participants who experienced an incident fatal IHD event had significantly ↓ baseline plasma PL concentrations of DHA and EPA than did matched controls (P=0.02). ↑ concentration of combined DHA and EPA was associated with a ↓ risk of fatal IHD (OR: 0.30 (95% CI: 0.12, 0.76; P=0.01). No association with non-fatal MI.	Dietary intake data not reported.

Lindqvist et al 2009 Study Design: Randomized Crossover Trial Class: A Rating:		N=35 healthy, but overweight men. Mean BMI: 28.3kg/m^2.	Subjects randomized to a six-week herring diet (150g baked herring fillets per day, five days per week) or reference diet (150g baked lean pork and chicken fillets per day, five days per week) with a 12-week washout period.	HDL was significantly ↑ with herring diet compared with reference diet: 1.04 vs. 0.99mmol per L. TAG ↓ after both diets, with NS difference between the two diets. ORACPCA values did not indicate ↓ concentrations of non-protein plasma antioxidants and oxidized LDL was not ↑ after the herring diet than after the reference diet.	None.
Mozaffarian 2008 Study Design: Systematic Review Class: M Rating:	Pooled analysis of RCTs and prospective cohort studies.	Four RCTs: 1. 2,033 English men with prior MI 2. 11,323 Italian subjects with recent MI 3. 3,114 Welsh men with chronic angina 4. 18,645 Japanese men and women with hypercholesterolemia. 15 prospective cohorts examined association between fish or n-3 FA intake and CHD death.	RCTs: Two servings per week oily fish or fish oil from one to 3g per day. Prospective cohorts: One to two oily fish servings per week or ~250-500mg EPA+DHA.	RCTs and prospective cohort studies provide concordant evidence that modest consumption of fish or fish oil (one to two servings per week oily fish or ~250mg per day EPA+DHA) substantially ↓ risk of CHD death and SCD. Pooled analysis of RCTs and prospective cohort studies shows the magnitude and dose-response of the effect: 36% ↓ risk of CHD death comparing zero and 250mg per day EPA+DHA consumption (P<0.001). Little additional benefit with higher fish intake.	None.
Mozaffarian D, Ascherio A et al, 2005 Study Design: Prospective 14-year follow-up study of dietary n-3 and n-6 intake assessed by administration of a self-administered validated FFQ at multiple time points and development of CHD assessed by biennial health history questionnaire. Class: B Rating:	Prospective 14-year follow-up study of dietary n-3 and n-6 intake assessed by administration of a self-FFQ.	N=45,722 male health professionals from the US. Location: United States.	Dietary n-3 and n-6 intake: Assessed by administration of a self-administered validated FFQ at baseline and every four years. Development of CHD assessed by biennial health history questionnaire.	↑ intake of EPA+DHA intake (>100mg per day) compared to ↓ intake (<100mg per day): • Associated with a 35% ↓ risk of sudden death (HR=0.65; 95% CI=0.47 to 0.88) • ↑ intake of EPA+DHA is associated with ↓ sudden death regardless of ALA level.	None.
Mozaffarian D, Psaty BM et al, 2004 Study Design: Prospective, population-based cohort study. Class: B Rating:	Follow up: 12-years.	N=4,815 adults. Age: ±65 years. Dietary intake assessed 1989 and 1990.	Consumption of tuna and other broiled or baked fish correlated with plasma phospholipid long-chain n-3 FAs, whereas consumption of fried fish or fish sandwiches (fish burgers) did not. Atrial fibrillation (AF) incidence prospectively ascertained on basis of	In multivariate analyses, consumption of tuna or other broiled or baked fish was inversely associated with incidence of AF, with 28% ↓ risk with intake one to four times per week (HR=0.72, 95% CI=0.58 to 0.91, P=0.005) and 31% ↓ risk with intake±5 times per week (HR=0.69, 95% CI=0.52 to 0.91, P=0.008) compared with <one time	

			hospital discharge records and annual electrocardiograms. During 12-year follow-up, 980 cases of incident AF were diagnosed.	per month (P trend=0.004). Results not different after adjustment for preceding MI or CHF. Fried fish or fish sandwich consumption was not associated with lower risk of AF.	
Mozaffarian D, Rimm EB 2006 Study Design: Meta-analysis or Systematic Review Class: M Rating:	Risk/Benefit analysis including pooled and meta-analysis.	Relationship between intake of fish and RR of CHD death in pooled analysis of prospective cohort RCTs evaluated non-parametrically using restricted cubic splines and adjusted for each within-study relationship.	RCTs: Two servings per week oily fish or fish oil from one to 3g per day. Prospective cohorts: One to two oily fish servings per week or ~250-500mg EPA+DHA.	Modest consumption of fish ↓ RR of CHD death and SCD by ≥25%. Higher intakes do not substantially further ↓ CHD mortality. This threshold effect explains findings among Japanese populations among whom additional n-3 PUFA intake results in little further ↓ in CHD death, as most of the population is above the threshold for maximum mortality benefits. At typical dietary intakes, anti-arrhythmic effects predominate, reducing risk of SCD and CHD death within weeks.	No detail provided on study populations in pooled analysis.
Panagiotakos et al 2007 Study Design: Prospective Study Class: B Rating:		N=542 (men 234; women 308). 79% participation rate. Age: 76+7 years (range 65-100 years). Location: Cyprus.	Fish intake and lipid profile, BP and blood glucose. Fish consumption was assessed by FFQs. • Zero: None or very rarely (<four units per month). • One: Rare (<four units or 150g per week) • Two: Moderate (Four to 12 units or 150 to 300g per week) • Three: Frequent (>12 units or >300g per week) Duration (in years) of eating fish. Mediterranean diet score. Physical activity measured.	90% reported consuming fish at least once per week, had the same fish habits for the past 30 years and types consumed mainly included small, lean fishes such as sardine, tope, anchovy, etc. After adjusting for confounders, fish intake inversely associated with SBP (P=0.026), fasting glucose (P<0.001), TC (P=0.012) and TG levels (P=0.024). Multinomial logistic regression revealed a ↓ of 100g per week in fish intake associated with a 19% (95% CI: one to 41) ↑ likelihood of having one additional cardiovascular risk factor (i.e., HTN, hypercholesterolemia, diabetes, obesity).	None.
Seierstad et al 2005 Study Design: Randomized controlled trial Class: A Rating:	6-week feeding period. 4 week run-in period.	58 adults with CHD (50 mails, 8 females). Age: 46-75 years. Attrition: 3.33%. Location: Norway.	*Fish Intake + n-3 FA* Consumed 700g per week of Atlantic salmon fillets for a 6-weeks in the following assigned three groups of n-3 PUFAs: Differently fed Atlantic salmon (700g per week), including: (1) 100% fish oil (2) 50% fish oil/50% rapeseed oil	Compared to fish and other n-3 FA: Salmon ↓ SBP, DBP and MAP by 4% (P<0.05) Total n-3 PUFAs and n-3/n-6 FA ratio, markedly ↑ in the 100% FO group (p=0.02) compared to all. Significant ↓ in serum TG and of VCAM-1 and IL-6 in subjects receiving 100% fish oil diet compared (P<0.05). Serum FA profiles of subjects after intervention	Anthropometric: Groups 1 and 3 differed in BMI (P=0.014).

			(3) 100% rapeseed oil. Before and after analyses: Serum FA profile; serum lipoproteins; markers of vascular inflammation.	mirrored those of the corresponding salmon fillets and respective salmon feeds. HDL-C significantly higher ($p<0.042$) at 6 weeks compared to baseline only in FO group. Serum TC were ↓ in all groups, significantly ($P<0.028$) only in the FO/RO group.	
Streppel et al 2008 Study Design: Longitudinal Cohort Study Class: B Rating:	Zutphen Study, cohort of men born between 1900 and 1920. Examined repeatedly between 1960 and 2000. Follow-up: 40 years.	N=1,373 men, born between 1900 and 1920; 348 men diet of CHD (66 died of SCD=19%). Mean survival age: 77 years. Location: The Netherlands.	Long-term EPA+DHA intake from fish and SCD. Men examined repeatedly between 1960 and 2000. Habitual food consumption collected by a Dutch adaptation of the cross-check dietary history method. Provides usual food intake pattern, six to 12 months preceding the interview. Interviews conducted by experienced dietitians. Up to seven repeated measures of fish consumption and EPA+DHA intake from fish collected over 40 years of follow-up. Total fish intake divided into fatty (salmon, mackerel, herring, eel and sardines) and lean (codfish, plaice and pollock) fish. Daily EPA+DHA intake calculated using Dutch food composition tables.	1,373 men participating in the Zutphen Study died from CHD (66 SCD=19% of all CHD deaths) Long-term fish consumer: 27% ↓ CHD death. Recent fish consumption not associated with CHD death. Inversely associated with CHD risk (P=0.16). The strength of the association ↓ from age 50 (HR=0.32, 95% CI: 0.13-0.80) until age 80 (HR=1.34, 95% CI: 0.58-3.12). Men with a daily EPA+DHA intake from fish <250mg compared with no intake, CHD death risk was ↓ to the same extent as for men with a daily intake >250mg (P for trend=0.27). Long-term fatty-fish intake (average 7g per day) ↓ SCD risk by 54%; no associations found with total and lean fish intake. Long-term fatty-fish intake ↓ the risk of CI: 0.27-0.78).	The number of SCD (66 events) observed in the Zutphen Study may have been too small to detect a dose-response relation for EPA+DHA intake. Could not account for Δ in product composition, due to lack of time-specific food composition tables needed to calculate nutrient intake over a longer period of time. Not possible to consider different methods of fish preparation like frying fat, which can affect a fish meal's FA composition and TFA which may ↑ cardiovascular risk. Information on fish consumption was missing for men newly included in the study in 1985 in the period 1960-1970 and had to be estimated.
Turunen et al 2008 Study Design: Cohort Study Class: B Rating:	Follow-up: 1980-2005.	N=4,487 fishermen and their wives. Location: Finland.	**Fish intake and CVD mortality** Fish consumption measured using self-administered semi-quantitative FFQ. Mortality rates recorded.	Fish consumption, serum long chain n-3 FA and environmental contaminants ↑ in the fishermen and wives than the general population. Fishermen and wives had ↓ mortality for all causes [standard mortality ratio (SMR)=0.78, 95% CI: 0.73-0.82 for fishermen, SMR=0.84, 95% CI: 0.76-0.93 for wives]. Fishermen and wives had ↓ mortality for IHD (SMR=0.73, 95% CI: 0.65-0.81 for fishermen, SMR=0.65, 95% CI=0.50-0.83 for wives). Mortality from cerebrovascular diseases and malignant neoplasm was ↓ among fishermen (SMR=0.67, 95% CI:	None.

				0.52-0.85, SMR=0.90, 95% CI: 0.80-1.01, respectively, for fishermen only), but not their wives.	
Virtanen et al 2008 Study Design: Prospective Cohort Study Class: B Rating:	Health Professionals Follow-up Study Follow-up: 18 years.	Health professionals aged 40-75 years. Location: United States.	**Fish and n-3 fatty acid intake and total major chronic disease.** Multiple validated FFQ over time used to compute cumulative averages of dietary intake. Fish intake based on 131-item food FFQ. Intake and amounts of four different seafood items: Canned tuna fish, dark meat fish (mackerel, salmon, sardines, bluefish and swordfish), other fish (not specified), and shrimp, lobster or scallops as a main dish. Fish intake in categories: five servings per week.	During 18 years of follow-up, 9715 (24.1%) major chronic disease events occurred: • 3,639 CVD events • 4,690 cancers • 1,386 deaths other causes. Baseline, mean (±SD) EPA+DHA intake was 0.3±0.2g per day and fish intake per day was 0.3±0.3g per day. Men with ↓ fish intake more likely to be physically active, have hypercholesterolemia and HTN, use aspirin and multivitamin supplements, drink more alcohol and smoke. Men with ↑ fish intake consumption: Have ↑ intakes of energy, PRO, EPA+DHA, PUFA, fiber, fruit, and vegetables and ↓ intakes of SFA, MUFA and TFA. Age-adjusted analyses: Fish intake inversely associated with risk of major chronic disease (P for trend=0.02). Multivariable adjustment: Neither fish nor dietary n-3 FA intake was significantly associated with risk of total major chronic disease. Compared with fish consumption of • Weekly intake of one serving and of two to four servings associated with a ↓ risk of total CVD by ~15%. • Fish intake >five servings per week not associated with ↓ risk. ↑ or ↓ n-6 FA intake: NS modification of the results (P for interaction more than 0.10).	Study population consisted of generally healthy men, the results may not be generalizable to women or to other populations. The databases used may not reflect the rapid Δ in the use of different types of vegetable oils in the food supply. Did not evaluate the potential effects of fish or EPA+DHA intake on other specific disease outcomes, such as heart failure, atrial fibrillation, that may be improved by fish intake.
Virtanen JK, Mursu J et al, 2009 Study Design: Prospective Cohort Study Class: B Rating:	Kuopio Ischemic Heart Disease Risk Factor Study. Average follow-up: 17.7 years.	N=2,682 men, free of AF at baseline (1984-1989). Younger and healthier; ↓ prevalence of CVD, DM, HTN and current smoking and ↑ education and income. Age: 42-60 years. Location: Finland.	**Fish, EPA and DHA intake and atrial fibrillation (AF).** Dietary intake of foods and nutrients assessed at the time of blood sampling by use of four-day food record. Serum esterified and non-esterified fatty acids were determined by gas	During 17.7 years of follow-up, 240 AF events. After adjustment for age and exam year, men in the highest serum EPA+DPA+DHA quartile had a 35% (95% CI 7% to 54%; P for trend=0.07) reduction in the HR of AF, compared with the lowest quartile (absolute risk in the	Sources of n-3 FA not documented. Participants in the study (KIHDRFS) did not visit the study site regularly, thus only AF events documented on discharge records are included and findings of the present study may apply only to hospitalized AF, which

			chromatography. All AF events that occurred between study entry and December 31, 2007 were included. Data on events obtained by record linkage from the national computerized Hospital registry. Cox proportional hazards regression models were used to estimate Hazard ratios (HRs).	reference group 13.4%; absolute risk ↓ 4.7%). Individual exam showed only DHA associated with ↓ risk; with a multivariable-adjusted HR of 38% ↓ (95% CI 8% to 58%; P for trend=0.02) in the highest quartile (reference group absolute risk 13.3%; absolute risk ↓ 5.1%). Mean serum ALA concentration=0.74% (SD 0.24%) of all FAs. No evidence that serum ALA was associated with the risk of AF. Multivariable-adjusted HRs (95% CI) in the serum ALA quartiles were one (ref), 1.26 (0.84 to 1.89), 0.74 (0.46 to 1.20), and 1.14 (0.72 to 1.79; P for trend -0.98), respectively. No association found when EPA+DPA+DHA concenration was ↓ (P for interaction=0.10), nor was there any evidence for interaction with EPA, DPA or DHA when evaluated individually (P for interactions=0.10).	may have weakened the associations. Serum DHA might only be a marker of a likelihood of being hospitalized for any cause. However, this is not supported by the lack of association between serum DHA and hospitalization for any cause during the follow-up in the post hoc analysis (HR in the highest vs. lowest serum DHA quartile 1.02, 95% CI 0.72 to 1.46, P for trend=0.76). Fish intake may have Δ during the follow-up. Use of a single measurement of serum long-chain n-3 PUFAs at baseline would underestimate its association with risk of AF. Thus the null results with ALA, a large proportion of which is oxidized, such that serum levels would depend more on recent intake. Observed association may be related to other factors associated with high serum long-chain n-3 PUFA concentration, such as in those consuming fish. No follow-up information about obesity, associated with arrhythmias. Several associations were evaluated, it is possible that the significant association found between serum DHA and risk of AF may have been due to type I error.
Wang et al 2006 Study Design: Systematic Review Class: M Rating: 		N=46 articles identified: • 14 RCTs • 25 prospective cohort • Seven case control. Secondary prevention trials: 11 RCTs: • Total subjects: N=19,403 • One prospective cohort study: Total N=415. Primary prevention trials: • One RCT • 25 cohort (N>340,000) • Seven case control. Three estimated ALA intake levels. Location: United States, Europe, China, Japan.	Fish, Fish oil and ALA intake and CVD. Comprehensive search 1966 to July 2005. Primary-prevention studies: Most estimated fish or fish-oil intakes.	After controlling for age, randomization to aspirin and β-carotene and coronary risk factors: Dietary fish intake was associated with a ↓ risk of sudden death, with an apparent threshold effect at a consumption level of one fish meal per week (P for trend=0.03).	No meta-analysis was conducted.

Whelton et al 2004 Study Design: Meta-analysis Class: M Rating:	Meta-analysis of observational studies to determine if fish consumption is associated with ↓ fatal and total CHD.	Total of 19 observational studies were included: 14 cohorts and five case-controls. Used Random Effects model.	Comparison between regular fish consumption and little to no fish consumption groups.	Fish consumption vs. little to no fish consumption was associated with an RR of 0.83 (95% CI 0.76 to 0.90; p <0.005) for fatal CHD RR=0.86 (95% CI 0.81 to 0.92; P<0.005) for total CHD.	No detail provided on study populations.
Yamagishi et al 2008 Study Design: Prospective Cohort Study Class: B Rating:	Average follow-up: 12.7 years.	N=57,972 men and women. Age: 40-79 years Location: Japan.	**Fish or omega-3 intake and risk of mortality from CVD** Self administered questionnaires: life-styles and medical histories of previous CVD or cancer. FFQ included 33 foods, including four fish items: Fresh fish, kamaboko (steamed fish paste), dried or salted fish and deep-fried foods or tempura (a common form of deep-fried fish or shellfish). Five choices for each item: Rarely; one to two days a month; one to two days a week; three to four days a week; and almost every day. Choices converted to scores of 0, 0.05 (1.5 of 30), 0.214 (1.5 of 7), 0.5 (3.5 of 7) and one, respectively. Quintiles of fish intake, media intake (g per day): • Men: 20, 33, 45, 62 and 86 • Women: 21, 33, 46, 62 and 85.	Number of events during 735,905 person-years of follow up: Documented 7,008 total death: • 419 due to IHD (including 329 MI) • 107 due to cardiac arrest • 307 due to heart failure • 972 due to stroke (including 223 intraparenchymal hemorrhages, 153 subarachnoid hemorrhages, and 319 ischemic strokes) • 2,045 total cardiovascular deaths. Inverse associations of fish and omega-3 PUFA intakes with risks of mortality from heart failure (multivariable HR for highest vs. lowest quintiles=0.76 [95% CI: 0.53 to 1.09] for fish and 0.58 [95% CI: 0.36 to 0.93] for n-3. Associations with IHD or MI relatively weak after adjustment for potential risk factors FA. Intakes of fish and n-3 PUFA were associated with 18% to 19%↓ risk of mortality from total CVD.	Type of fish consumed not reported. Underestimated number of times fish was eaten for people in the upper quadrants; potential for under reporting (e.g., authors reported fish intake of 49.5g per day, which is lower than the National Nutrition Survey in 1990 (95.3g per day). High number of exclusion (39%) incomplete dietary information; excluded subjects were older and more likely to be men than women compared with included subjects. Healthy lifestyles or socioeconomic status are possible residual confounding by other factors.

Research Design and Implementation Rating Summary
For a summary of the Research Design and Implementation Rating results, click here.

Worksheets

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